REMARKS

Claims 1-11 and 61-62 are pending in this application. No claim amendments are made in this paper.

I. Information Disclosure Statement

The Examiner alleges that "Applicant should note that simply citing a reference in applicant's arguments is not sufficient for Office consideration. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office. Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered." (Office Action, page 2).

Applicants submit herewith a Supplemental Information Disclosure Statement and revised form 1449 entitled "List of References Cited by Applicant." The revised form 1449 lists two (2) references for the Examiner's review and consideration. Applicants respectfully request that the Examiner review the references and make them of record.

II. The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

The Examiner has maintained the rejection of claims 1-11 under 35 U.S.C. § 103(a) as allegedly unpatentable over Marx, Pitot, and Priel in combination. (Office Action, page 2). In addition, the Examiner rejects claims 61-62 as allegedly unpatentable over Marx, Pitot, and Priel in combination. (Office Action, page 6).

Applicants respectfully traverse these rejections.

Applicants respectfully submit that 1) the Examiner has not established a *prima facie* case of obviousness, and 2) even if, *arguendo*, a *prima facie* case of obviousness were established, sufficient unexpected results are provided to rebut any presumption of obviousness.

1. The Examiner has not established a *prima facie* case of obviousness.

The Examiner has rejected the pending claims as allegedly unpatentable over Marx, Pitot, and Priel in combination because "the use of materials in combination, each of which is known to function for intended purpose, is prima facie obvious." (Office Action, page 7). In this regard, the Examiner relies on the alleged precedent set forth in *Ex parte Quadranti*, 25 U.S.P.Q.2d 1071 (Bd. Pat. Appl. & Inter. 1992).

Applicants respectfully submit that the Examiner is improperly applying *Ex parte Quadranti* to the present invention.

The applicability of *Ex parte Quadranti* is dependent upon the facts of each particular case, and care must be taken not to apply the case broadly. Moreover, there still must be a motivation to combine the references and a reasonable expectation of success. "Although a reference need not expressly teach that the disclosure contained therein should be combined with another...the showing of combinality, in whatever form, must nevertheless be clear and particular." *Winner International Royalty Corp. v. Wang*, 202 F.3d 1340, 1348-49, 53 U.S.P.Q.2d 1580 (Fed. Cir. 2000) (emphasis added). As noted in *Yamanouchi Pharmaceutical Co. v. Danbury,* 231 F.3d 1339, 1343, 56 U.S.P.Q.2d 1641 (Fed. Cir. 2000):

> Virtually all inventions are combinations of old elements. Therefore, an examiner...may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner...to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. (emphasis added).

For example, in *Ex parte Bokisa*, the Board of Patent Appeals and Interferences acknowledged but refused to apply the very rule relied upon by the Examiner[1] for the present

[1] The Board specifically acknowledged but refused to apply the rule that "[i]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose."

invention because there was no motivation to combine the prior art references. 1997 WL 1897871 (Bd. Pat. Appl. & Inter. 1997).[2] Specifically, even though the combined materials were individually useful for the same purpose, the Board held that one of ordinary skill in the art would not have found obvious the combination of prior art references because of known "undesirable effects" of one of the combined materials. *Id.*

Further, in *Yamanouchi*, the Court indicated that a reasonable expectation of success in a pharmacological context involves consideration of side effects and toxicity. 213 F.3d at 1345; *see also, Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d. 1961 (Fed Cir. 2003) ("there can be little better evidence negating an expectation of success than actual reports of failure").

As pointed out in Applicants' previous responses, topoisomerase inhibitors were known to be associated with various side effects such as gastrointestinal toxicities. *See e.g.*, Hecht, *Oncology*, 12(8 Suppl. 6): 72-8 (1998) (attached as Exhibit B).[3] Thus, because of these undesirable effects, Applicants respectfully submit that a person of ordinary skill in the art would not have been motivated to use thalidomide in combination with a topoisomerase inhibitor.

Further, as pointed out in Applicants' previous responses, thalidomide was not an approved anti-cancer drug at the time of the invention.[4]

In response, the Examiner has stated that "Applicant should note that FDA approval or approval for any other U.S. agency is not required under 35 U.S.C. 103." (Office Action, page 4). Applicants agree that a showing of FDA approval is not required to overcome an obviousness rejection under 35 U.S.C. § 103. This aside, Applicants respectfully submit that the lack of FDA approval shows that one of ordinary skill in the art had better alternatives to thalidomide, and thus, would have been led away from using thalidomide in combination with any other agent, much less a topoisomerase inhibitor.

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[2] Attached as Exhibit A for the Examiner's convenience.

[3] Provided in the Supplemental IDS, which is being filed concurrently herewith.

[4] The Examiner has indicated that "it is unclear what type of approval applicant is referring to." (Office Action, page 4). Applicants are referring to FDA approval.

In this regard, Applicants respectfully direct the Examiner's attention to *Yamanouchi*. In *Yamanouchi*, the Court held that the selection of a compound for use in a combination was not obvious even though the compound exhibited activity that was three times greater than the benchmark. 231 F.3d at 1345. Specifically, the Court held that the required motivation to use the compound was not shown in light of better alternatives that were up to ten times more active than the benchmark, stating that "other more active compounds would have been the obvious choices." *Id.* Thus, Applicants respectfully submit that rather than using an unapproved drug, the obvious choice for one skilled in the art would be any of the numerous approved anti-cancer drugs that were available at the time of the invention.

The Examiner also alleges that the lack of approval is irrelevant because Marx teaches the anti-tumor activity of thalidomide and "[t]he disclosure of Marx is seen to pre-date applicant's earliest claim of priority and thus constitutes prior art as applied under recited statute." (Office Action, page 4). However, as the Examiner is well aware, the art as a whole must be considered. In this regard, Applicants respectfully submit that despite the disclosures of Marx, the prior art as a whole would not have motivated those of ordinary skill in the art to use the combination of thalidomide and topoisomerase inhibitors because 1) cancer treatments other than thalidomide were available at the time of this invention; and 2) topoisomerase inhibitors were known to be associated with various side effects such as gastrointestinal toxicities. The Examiner does not provide any evidence whatsoever as to whether specific motivation to combine thalidomide and topoisomerase inhibitors existed at the time frame of this invention.

In sum, Applicants respectfully submit that the Examiner has improperly applied *Ex parte Quadranti* to the present invention, and thus, has not established a *prima facie* case of obviousness. Moreover, a person of ordinary skill in the art would not have had the legally required motivation or expectation of success to combine thalidomide with a topoisomerase inhibitor.

For at least the foregoing reasons, Applicants respectfully request that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn.

2. Sufficient unexpected results were provided.

In previous responses, Applicants have pointed out that the specification discloses an unexpected synergy between thalidomide and a topoisomerase inhibitor (*e.g.*, irinotecan). Specifically, the specification discloses that when thalidomide is co-administered with irinotecan to patients with metastatic colorectal cancer, a remarkable absence of gastrointestinal toxicity typically associated with irinotecan individually is observed. (Specification, page 31, line 24 - page 32, line 21). .

Despite this surprising result provided in the specification, the Examiner has maintained the allegation that "if applicant wishes to use an argument of unexpected results for overcoming the instant rejection, applicant's showing should be commiserative [sic: commensurate] with the scope of the claims." (Office Action, page 4). In addition, the Examiner has again stated that "the features upon which applicant relies (*i.e.*, co-administration of thalidomide and irinotecan to patients with colorectal cancer) are not recited in the rejected claims(s)." *Id.* Further, the Examiner has maintained the allegation that "[a]lthough the claims are interpreted in light of the specification, limitations from the specification are not read into the claims." (Office Action, page 4). In this regard, the Examiner cites *In re Van Geuns*, 988 F.2d 1181, 26 U.S.P.Q.2d 1057 (Fed. Cir. 1993) and appears to be relying on language taken directly from the MPEP § 2145.

However, Applicants respectfully submit that the Examiner has misinterpreted the meaning of the rule cited by the MPEP and established by *In re Van Geuns*. In *In re Van Geuns*, the senior party, in an attempt to overcome an obviousness rejection, argued that their own claim was limited to only the limitations described in the specification. 988 F.2d at 1184. Specifically, while the senior party's claim recited a magnet assembly with a "uniform magnetic field," the senior party argued that this claim was limited to only NMR and MRI magnets, which were listed in the specification. *Id.* The Court subsequently refused to limit the scope of the claim to the limitations of the specification and held that the claims encompassed a broader scope for purposes of determining obviousness.

In stark contrast, the facts here are exactly opposite to those in *Van Geuns*. Unlike the senior party in *Van Geuns*, Applicants are <u>not</u> arguing that limitations from the specification should be read into the claims. That is, while the senior party in *Van Geuns* argued that their

claim was limited to only NMR and MRI magnets, Applicants are not arguing that the scope of the pending claims is limited to the co-administration of thalidomide and irinotecan to patients with colorectal cancer. Quite to the contrary, Applicants maintain that they are entitled to the full scope of the claims as presented. Thus, Applicants respectfully submit that *Van Geuns* is inapplicable to the present invention, and the Examiner has not provided any legal basis to support his position. To the extent that Applicants are not arguing that limitations from the specification should be read into the claims, the Examiner's allegation that "limitations from the specification are not read into the claims" is irrelevant to the patentability of the present invention, and thus, is an improper basis for rejection. (Office Action, page 4).

Further, Applicants respectfully point out that non-obviousness of a broader claimed range or genus may be proven by a narrower range of data or species. For example, in *In re Kollman*, the Court held that data showing the success of herbicides within only part of the claimed ranges were sufficient to rebut a PTO holding of *prima facie* obviousness because "one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof." 595 F.2d 48, 56, 201 U.S.P.Q. 193 (C.C.P.A. 1979).

In this regard, Applicants have disclosed a working example showing the unexpected synergy between thalidomide and irinotecan. Furthermore, in the previous response, Applicants directed the Examiner's attention to *BioWorld Today*, November 4, 2005, page 2 (hereafter "BioWorld article") (attached as Exhibit C).[5] This article reported that the combination of thalidomide and topotecan has an improved efficacy and safety in the treatment of epithelial ovarian cancer as compared with topotecan alone. Thus, in view of the synergistic effects of two different topoisomerase inhibitors individually used in combination with thalidomide in two different cancer types, one of ordinary skill in the art could "ascertain a trend" and "reasonably extend" the results to the entire scope of the pending claims. *In re Kollman*, 595 F.2d at 56. Thus, Applicants respectfully submit that any presumption of obviousness is rebutted, and Applicants are entitled to the full scope of the claims as presented.

[5] Also provided in Supplemental IDS, which is being filed herewith.

Further, Applicants respectfully submit that the Examiner has not provided any factual basis that evidences that the synergistic effect observed between thalidomide and irinotecan or topotecan cannot be extended to the entire scope of the claims.[6] Therefore, to the extent that no factual basis in the record that shows the combination of thalidomide and other topoisomerase inhibitors would "behave differently" than the combination of thalidomide and irinotecan or topotecan , Applicant respectfully requests that this rejection be withdrawn.

In sum, Applicants respectfully submit that even if, *arguendo*, a *prima facie* case of obviousness exists, Applicants have disclosed unexpected results that rebuts any presumption of obviousness. Specifically, Applicants have disclosed that when thalidomide is co-administered with irinotecan to patients with metastatic colorectal cancer, a remarkable absence of gastrointestinal toxicity typically associated with irinotecan individually is observed. Further, the *BioWorld* article discloses that the combination of thalidomide and topotecan has an improved efficacy and safety in the treatment of epithelial ovarian cancer. In view of these unexpected results, Applicants respectfully submit that the whole scope of the pending claims is unobvious over prior art of record.

For the foregoing reasons, Applicants respectfully request that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn.

III. Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and thus, request that the rejections be withdrawn.

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[6] In this regard, the Examiner alleges that "[a]rguing '[t]hose of ordinary skill in the art would have had no reason to believe that such synergism would not extend to the combination of thalidomide and other topoisomerase inhibitors...or types of cancer other than colorectal cancer' is not sufficient." (Office Action, page 4). However, Applicants respectfully point out that such a fact is indeed sufficient, based on well-established principles. *See, e.g. In re Crescon*, 474 F.2d 1331, 1334 (C.C.P.A. 1973) (*prima facie* case of obviousness for a claim that recited the use of a compound in an inert solvent or substrate was rebutted in view of unexpected results showing the claimed compound's use in benzene because "no factual basis appears in the record for expecting the compound to behave differently in other environments.") (emphasis added).

No fee is believed due for the submission of this paper. However, if any fees are due for the submission of this paper or to avoid abandonment of this application, please charge them to Deposit Account No. 50-3013.

Respectfully submitted,

Date: August 21, 2006

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1997 WL 1897871 (Bd.Pat.App & Interf.)

(Cite as: 1997 WL 1897871 (Bd.Pat.App & Interf.))

*1 THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

Board of Patent Appeals and Interferences

Patent and Trademark Office (P.T.O.)
EX PARTE GEORGE S. BOKISA
Appeal No. 95-1549
Application 07/849,466 [FN1]
April 10, 1997

Armand P. Boisselle

Kenner, Otto, Boisselle and Sklar

The Keith Building

1621 Euclid Avenue, Nineteenth Floor

Cleveland, OH 44115

Before KIMLIN, GARRIS and THIERSTEIN

Administrative Patent Judges.

THIERSTEIN

Administrative Patent Judge.

ON BRIEF

DECISION ON APPEAL

This is an appeal from the final rejection of claims 1 through 25, all the claims in the application.

Claims 1, 17 and 24 are illustrative of the subject matter on appeal and read as follows:

1. An aqueous acidic solution for plating tin, lead or tin-lead alloys on a substrate which comprises

(A) at least one bath-soluble metal salt selected from the group consisting of stannous salts, lead salts, or a mixture of stannous and lead salts;

(B) an acid from the group consisting of sulfuric or fluoboric acid; and

(C) at least one soluble bismuth salt of an alkane sulfonic acid or an alkanol sulfonic acid in an amount to provide a solution containing less than about 10 grams per liter of bismuth ions.

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17. The plating bath of claim 12 wherein the bismuth salt (C) is prepared by dissolving bismuth oxide in an alkane sulfonic acid.

24. A method of electrodepositing tin, lead or tin-lead alloy on a substrate which comprises electroplating said substrate in the aqueous plating bath of claim 1.

The references relied on by the examiner are:

Nobel et al. (Nobel)	4,871,429	Oct. 3, 1989
Wilson	5,039,576	Aug. 13, 1991

The claims stand rejected as follows:

I. Claims 1 through 16 and 18 through 25 stand rejected under 35 U.S.C. § 103 over Nobel;

II. Claim 17 stands rejected under 35 U.S.C. § 103 over Nobel in view of Wilson.

We reverse.

OPINION

1. Background

As seen from independent claims 1, 12 and 21 on appeal, appellant's invention involves an aqueous acidic solution for plating alloys on a substrate. The solution in claim 1 comprises either sulfuric acid or fluoboric acid with a bath-soluble plating tin, lead or tin-lead salt(s) and at least one soluble bismuth salt of an alkane sulfonic acid or an alkanol sulfonic acid. The solution in independent claim 12 is essentially the same as claim 1 except that the bath-soluble metal salt is limited to tin. Claim 17, wherein the bismuth salt is prepared by dissolving bismuth oxide in an alkane sulfonic acid, depends from claim 12. Claim 21 is essentially the same as claim 12 with additional limitations on the amounts of each component in the bath or solution. Claims 24 and 25 are directed to a method of electrodepositing tin or tin-lead on a substrate using the solutions of claim 1 and claim 21 respectively.

***2** Nobel teaches baths and methods for electroplating tin or tin-lead alloys. These baths contain soluble tin and/or lead metals as salts of alkyl or alkylol sulfonic acid, a soluble alkyl or alkylol sulfonic acid, at least one wetting agent, and a hydroxyl phenyl compound reducing agent to prevent or limit the formation of oxidized tin or sludge during electroplating. Nobel also teaches, generally, a soluble bismuth compound for use in these baths, especially naming bismuth nitrate as an acceptable example.

Nobel formulates plating solutions for tin and tin alloys prepared with metal fluoborates and free fluoboric acid wherein anti-oxidants are incorporated but teaches that "[i]n spite of the fact that the known anti-oxidants are incorporated into these fluoboric acid formulations, experience in high-speed plating applications has shown that large quantities of tin sludge are nevertheless formed

during electrolysis." (Nobel, column 2, lines 3-7.) Numerous examples are provided in Nobel showing this undesirable oxidation of tin in tin plating formulations and rapid development of sludge in plating formulations using a fluoborate based mixture of tin and lead in a bath with an excess of free fluoboric acid (see Nobel, examples 1, 3 and 5).

The fluoborate-based baths are compared to the baths using free methyl or methylol sulfonic acid where oxidation of tin, present as a methane sulfonate salt, is substantially reduced and the build-up of sludge from the mixture of tin and lead, also present as methane sulfonate salts, is minimal (see Nobel, examples 1, 2, 4 and 6).

There is no mention of sulfuric acid in Nobel.

Wilson, column 5, lines 28-29, is relied upon by the examiner for teaching a preparation for a bismuth ion by a reaction of bismuth trioxide with methane sulfonic acid (answer, page 4, lines 6-7).

2. The § 103 Rejections

The first issue to be considered here is appellant's contention that the examiner has failed to establish a prima facie case of obviousness with regard to the rejection of claims 1-16 and 18-25 (brief, page 5, lines 14-15). In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent." [Citations omitted.]).

A difference common to the plating baths disclosed in Nobel when compared to the plating baths of independent claims 1, 12 and 21 is that in Nobel's baths each of (1) fluoboric acid and (2) methyl or methylol sulfonic acid or acid salt(s) is employed separately rather than together whereas the claimed baths contain a combination of (1) fluoboric acid and (2) alkane or alkanol sulfonic acid salt(s) of bismuth.

The court states in In re Geiger, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987) that "[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)."

***3** The examiner fails to provide a specific teaching in Nobel to the claimed combination. Moreover, we find no teaching, suggestion or incentive in Nobel to modify the fluoboric acid containing baths it discloses by the addition of alkyl or alkylol sulfonic acid salt(s) or to modify the baths containing alkyl or alkylol sulfonic acid salt(s) by the addition of fluoboric acid. There is no rationale in the rejection that overcomes these deficiencies.

In the absence of any support in Nobel for the claimed combination, the examiner states in the answer on page 4, beginning in the last line, that:

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[I]t would be [sic: have been] obvious to one of ordinary skill in the art at the time the invention was made to use both alkane or alkanol sulfonic acid and fluoboric acid in tin plating baths of Nobel because it has been held to be obvious to use a mixture of two materials each of which has been used separately for the same purpose, In re Kerkhoven, [626 F.2d 846, 850,] 205 USPQ 1269, [sic: 1069,] 1072 (CCPA 1980).

The examiner's reliance upon Kerkhoven shows a belief that the decision is relevant. We disagree. The court in Kerkhoven, 626 F.2d at 850, 205 USPQ at 1072 states:

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. In re Susi, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); **In re Crookett, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (1960)**. As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art. In the case at bar, appealed claims 2-4, 9 and 14 require no more than the mixing together of two conventional spray-dried detergents. Thus, these claims set forth prima facie obvious subject matter.

These are not the facts before us. Nobel provides both a teaching and evidence that the use of fluoboric acid in tin or tin-lead plating baths is associated with an undesirable formation of oxidized tin or of sludge from tin and lead. At the same time, Nobel contrasts this undesirable formation with substantially less of oxidized tin or sludge in baths using methyl or methylol sulfonic acid and acid salts. See appellant's statement that:

In fact, Nobel compares his plating baths with tin plating baths containing tin fluoborate and fluoboric acid (Examples 1A, 3 and 5) and demonstrates that the fluoboric acid containing plating baths provide undesirable results. [Brief, page 6, lines 1-3.]

One of ordinary skill in the art would not have found obvious the combination of a fluoboric acid containing plating solution exhibiting undesirable effects with an alkyl or alkylol sulfonic acid salt containing plating solution that minimizes these effects.

Our disagreement regarding the relevance of Kerkhoven continues in the face of the dissenting opinion.

***4** The combination of the plating baths suggested by the dissent does not flow from the teachings in Nobel showing a difference in the precipitation for fluoboric acid and alkyl or alkylol sulfonic acid even at low temperatures in example 1. Clearly, the purpose of Nobel's disclosure is to contrast the effect of the named antioxidants in a comparison of the plating baths. The effect of the comparison is to view each plating bath as having different characteristics. As pointed out by the dissent, even at low temperatures one causes more precipitation than the other. One of ordinary skill in the art would not have combined a plating bath causing more precipitation with one causing less. Kerkhoven is not applicable on these facts.

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Moreover, the dissent's position concerning the addition of bismuth in the form of a sulfonic acid salt is inapposite to the facts in Kerkhoven. At best under Kerkhoven a combination of the plating baths referred to by the dissent would accomplish a combination of fluoboric acid and alkyl or alkylol sulfonic acid. A second line of reasoning must be addressed to add a bismuth salt to the combination.

On this issue we also have a position contrary to that of the dissent. One of ordinary skill in the art would not have added a bismuth salt of an alkane or alkanol sulfonic acid in view of the teaching in Nobel cited by the dissent in the sentence bridging pages 13 and 14 that the bismuth compounds useful in the invention "are those which are water or solution soluble and the anion produced by the bismuth compound should not interfere with the tin or lead salts, such as causing precipitation thereof (column 8, lines 12-18)." As the dissent points out, at low temperatures EXAMPLE 1 in Nobel shows sludge is formed by the methane sulfonic acid anion in a tin plating bath. This would have led an ordinarily skilled artisan to expect that a bismuth salt of sulfonic acid would also form sludge and thus should not be used because it would "interfere with the tin ... salts, such as causing precipitation thereof."

With respect to the claimed sulfuric acid, clearly, the examiner provides no teaching, suggestion or incentive to modify the baths of Nobel with this acid since there is no mention of the acid in Nobel.

Thus, notwithstanding the opinion of the dissent, we conclude that the examiner has not established a prima facie case of obviousness with regard to the invention of claims 1-16 and 18-25 on appeal.

With regard to dependent claim 17, we have reviewed the examiner's rejection of the claim under 35 U.S.C. § 103 over Nobel in view of Wilson. However, even if Nobel were modified by Wilson in the manner proposed by the examiner, the rejection would still be deficient for the reasons discussed above with respect to independent claim 12 from which claim 17 depends.

Accordingly, we cannot sustain the § 103 rejection of claims 1-16 and 18- 25 over Nobel or the § 103 rejection of claim 17 over Nobel in view of Wilson.

***5** Because we reverse on the basis of failure to establish a prima facie case of obviousness, we need not reach the issue of the sufficiency of the showing of unexpected results. In re Geiger 815 F.2d at 688, 2 USPQ2d at 1278.

We reverse the decision of the examiner.

REVERSED

BOARD OF PATENT APPEALS AND INTERFERENCES

BRADLEY R. GARRIS

Administrative Patent Judge

1997 WL 1897871 (Bd.Pat.App & Interf.)

(Cite as: 1997 WL 1897871 (Bd.Pat.App & Interf.))

JOAN THIERSTEIN

Administrative Patent Judge

FN1. Application for patent filed March 11, 1992.

DISSENTING OPINION

KIMLIN

Administrative Patent Judge

I respectfully disagree with the conclusion reached by the majority. In my view, the examiner properly found that the claimed subject matter would have been prima facie obvious to one of ordinary skill in the art in view of the prior art of record, and that the Rule 1.132 Declaration by the present inventor, George Bokisa, does not establish unexpected results for the claimed invention. [FN2]

Like appellant, Nobel discloses an aqueous acidic solution for plating tin or tin-lead alloys which comprises stannous salts, an acid, a source of alkyl or alkylol sulfonate anions and a source of bismuth cations. Nobel does not expressly disclose the presently claimed bismuth salt of an alkane sulfonic acid or an alkanol sulfonic acid as the source of bismuth cation. In addition, although Nobel evidences that it was known in the art to use fluoboric acid in a tin plating solution, which fact is acknowledged in the present specification, the reference does not disclose the combined use of fluoboric acid and a source of alkyl or alkylol sulfonate anions, as presently claimed. [FN3] It is my opinion that these claimed distinctions would have been obvious to one of ordinary skill in the art within the meaning of § 103 in view of the teachings of the prior art.

Regarding the claimed bismuth salt of an alkane sulfonic acid or an alkanol sulfonic acid, we agree with the examiner that, inasmuch as Nobel teaches plating solutions for tin or tin-lead alloys comprising bismuth cations and alkane or alkanol sulfonate anions, it would have been prima facie obvious to one of ordinary skill in the art to employ a bismuth salt of an alkane sulfonic acid or an alkanol sulfonic acid as the single source of both of the required ions. While Nobel exemplifies bismuth nitrate as the source of bismuth ion, the reference is not limited to such. Nobel teaches that bismuth compounds useful in the invention to improve the low current density of the deposits "are those which are water or solution soluble and the anion produced by the bismuth compound should not interfere with the tin or lead salts, such as causing precipitation thereof" (column 8, lines 12-18). The obviousness of using the claimed bismuth salt of an alkane sulfonic acid or an alkanol sulfonic acid is further supported by Wilson's use of such (bismuth methane sulfonate) in a similar plating bath, as acknowledged at page 2 of appellant's specification.

***6** I do not find that the Rule 1.132 Declaration of the present inventor establishes unexpected results for the claimed invention. The declaration is presented to demonstrate that, when the claimed bismuth salt of methane sulfonic acid is used instead of bismuth nitrate, an unexpected and significant improvement

in thickness of the tin coating is realized at low current density. However, the probative value of the declaration evidence is not commensurate in scope with the degree of protection sought by the appealed claims. In re Grasselli, 713 F.2d 731, 743, 218 USPQ 769, 778 (Fed. Cir. 1983); In re Clemens, 622 F.2d 1029, 1035, 206 USPQ 289, 296 (CCPA 1980). This is so because the comparative experiment of the declaration used sulfuric acid instead of fluoboric acid and, as noted above, sulfuric acid is not a requirement of the claimed solution. Appealed claim 1 encompasses a plating solution comprising fluoboric acid, and there is no evidence of record which establishes that, when fluoboric acid is used in conjunction with a bismuth salt of methane sulfonic acid, similar results occur. In addition, the declaration does not provide a comparison with the closest prior art. In re Johnson, 747 F.2d 1456, 1461, 223 USPQ 1260, 1264 (Fed. Cir. 1984). Nobel discloses the use of fluoboric acid and alkyl or alkylol sulfonic acid, not sulfuric acid. Furthermore, appellant has not established the statistical validity of the conclusion drawn from the declaration data. The declaration reports only a single comparative run. There is no evidence that the reported results are reproducible. We find this especially significant since Nobel and other prior art of record teach that bismuth nitrate improves the low current density of the deposits, and the declaration data shows virtually no improvement for a plating solution comprising bismuth nitrate as compared to a solution comprising no bismuth at all. Hence, the single test run offered by appellant produces a result that is contrary to the teaching of the prior art.

I also agree with the examiner that since Nobel discloses the use of either fluoboric acid or methyl sulfonate in plating solutions for tin or tin-lead alloys, it would have been obvious for one of ordinary skill in the art to utilize a plating solution comprising both fluoboric acid and methyl sulfonate or methane sulfonic acid. Much is made by appellant and the majority that Nobel shows that the use of fluoboric acid, unlike the sulfonic acid, results in the undesirable rapid development of sludge. However, when Nobel is read in its entirety, it can be seen that fluoboric acid only presents a sludge problem when employed in high-speed plating applications at elevated temperatures (see paragraph bridging columns 1 and 2). The table of Nobel's EXAMPLE 1 shows that fluoboric acid only causes a sludge problem at temperatures of 120° F and 140° F, but not at 80° F, which lower temperature, significantly, is approximately the temperature utilized by appellant in the plating methods exemplified in the present specification. According to EXAMPLE 1 of Nobel, when pyrocatechol is used as the antioxidant, less sludge (4.5%) is formed by fluoboric acid at 80° F than by methane sulfonic acid (5.5%). In my view, one of ordinary skill in the art would readily glean from Nobel that when plating at lower temperatures, as appellant does, one may employ fluoboric acid, methane sulfonic acid or a combination thereof without expecting the undesirable formation of sludge. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980). Appellant's specification does not make mention of a sludge problem when using fluoboric acid and, based on the Nobel disclosure, this would seem expected by one of ordinary skill in the art due to the low operating temperatures of appellant's plating solutions.

***7** The majority states that the "examiner fails to provide a specific teaching in Nobel to the claimed combination" of fluoboric acid and alkyl or alkylol sulfonic acid salts, and that they find no teaching, suggestion or incentive in

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Nobel to modify the disclosed baths by combining the acids in one bath (page 6 of decision). However, as stated by the court in Kerkhoven, 626 F.2d at 850, 205 USPQ at 1072, which is quoted by the majority, "[a]s this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art." Manifestly, the combination of acids need not be taught by Nobel for a finding of obviousness. An incentive for the combination of acids would be the unavailability of a sufficient amount of one of the acids, or the higher cost of one of the acids.

The majority makes the point at page 9 of the decision that, since EXAMPLE 1 of Nobel shows that one bath causes more precipitation than the other, one ""would not have combined a plating bath causing more precipitation with one causing less." I respectfully consider this a myopic view of the example's tabulated results. When the amount of oxidized tin generated in all solutions at 80° F is compared to the undesirable amount of oxidized tin produced at 120° F and 140° F by solutions comprising fluoboric acid, it can be readily seen that all solutions, including those comprising fluoboric acid and either antioxidant, generate acceptable levels of oxidized tin.

I disagree with the majority that my "position concerning the addition of bismuth in the form of a sulfonic acid salt is inapposite to the facts in Kerkhoven" (page 9). I do not cite Kerkhoven in support of the obviousness of adding the claimed bismuth salt. Also, merely because Kerkhoven is not on "all fours" with the facts of the present case does not mean that the principle espoused therein is not apposite for the proposition for which I applied it, viz., the combination of the relevant acids in the plating solution. Certainly, the majority does not mean to suggest that Kerkhoven is applicable only when there is just one distinction between a claimed invention and the prior art.

Regarding the majority's view that the skilled artisan would have expected a bismuth salt of sulfonic acid to form sludge due to Nobel's example at low temperatures, I again point out that one would have gleaned from the example that the amounts of sludge produced at low temperatures are acceptable. I emphasize that appellant's specification is not directed to the prevention of sludge, and there is no assertion by appellant, let alone any evidence of record, which indicates that appellant's plating bath, at low temperatures, generates any less sludge than that amount which would have been predicted by the example of Nobel.

For the above stated reasons, I find that the claimed subject matter would have been obvious to one of ordinary skill in the art and, therefore, I would sustain the examiner's rejection.

BOARD OF PATENT APPEALS AND INTERFERENCES

***8** EDWARD C. KIMLIN

Administrative Patent Judge

FN2. Although appellant submits at page 3 of the Brief that each of the appealed claims is considered to be separately patentable, appellant's Brief advances

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separate arguments for only claims 1-23, as a group, and claims 24 and 25, as a group.

FN3. We note that claim 1 on appeal defines the acid as one selected from the group consisting of sulfuric or fluoboric acid. Accordingly, claim 1 does not require the presence of sulfuric acid, i.e., claim 1 embraces plating solutions comprising fluoboric acid as the sole acid. That the examiner provides no teaching or suggestion to modify the baths of Nobel with sulfuric acid, as pointed out by the majority, is irrelevant to the rejection of the subject matter embraced by claim 1.

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Gastrointestinal Toxicity of Irinotecan

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ABSTRACT:
Irinotecan (CPT-11 [Camptosar]) is an important new chemotherapeutic drug that demonstrates activity against a broad spectrum of malignancies, including carcinomas of the colon, stomach, and lung. Unfortunately, frequent and often severe gastrointestinal toxicities, particularly diarrhea, have limited its more widespread use. A cholinergic syndrome resulting from the inhibition of acetylcholinesterase activity by irinotecan is frequently seen within the first 24 hours after irinotecan administration but is easily controlled with atropine. Late diarrhea occurs in the majority of patients, however, and is National Cancer Institute (NCI) grade 3 or 4 in up to 40%. The late syndrome appears to be related to the effects on the bowel of SN-38, the active metabolite of irinotecan, which undergoes biliary excretion and inactivation. Early recognition and treatment of late diarrhea with high-dose loperamide have reduced, although not entirely eliminated, patient morbidity. Further study is needed to identify the mechanism of irinotecan-induced late diarrhea and to evaluate potential new therapies. [ONCOLOGY 12(Suppl 6):73-78, 1998]

Introduction

Irinotecan (CPT-11 [Camptosar]) is an important new drug in the chemotherapeutic armamentarium. Irinotecan is active against a broad spectrum of malignancies, including carcinomas of the colon, stomach, and lung. Unfortunately, frequent and often severe gastrointestinal toxicities, particularly diarrhea, have limited its more widespread use.

Clinical observations, preclinical models, and pharmacokinetic studies have yielded some critical insights into the pathophysiology of these side effects. Early recognition and treatment of these toxicities have resulted in a reduction in patient morbidity. Despite these new pathophysiologic insights and advances in treatment, gastrointestinal toxicities remain a major problem with the clinical use of irinotecan. The gastrointestinal side effects of irinotecan administration can be divided into two distinct syndromes: early and late.

Early Diarrhea/Cholinergic Syndrome

Early toxicity occurs within the first 24 hours of irinotecan administration and is characterized by diarrhea, emesis, diaphoresis, abdominal cramping, and, less commonly, hyperlacrimation and rhinorrhea.[1] Various components of the syndrome have been reported in up to 80% of patients receiving the drug.[2,3]

The spectrum of symptoms appears to be dose-related. Patients who receive lower doses experience abdominal cramping, diarrhea, and diaphoresis, while those given over 300 mg/m^2 also complain of salivation, hyperlacrimation, and visual changes.[4] In a study of patients treated with 250 mg/m^2 of irinotecan every 2 weeks, Petit et al found that most symptoms occurred within the first 2 hours, and median duration was approximately 30 minutes.[5]

The constellation of early symptoms is consistent with cholinergic hyperstimulation. Irinotecan has been shown to mimic the effects of acetylcholine in various in vitro preparations.[6] This action is mediated by inhibition of acetylcholinesterase and, perhaps less importantly, by direct binding to and stimulation of muscarinic receptors (Figure 1).[7]

In both animal models and humans, symptoms are inhibited by administration of the anticholinergic drug atropine.[8] Atropine as needed is now routinely used in patients treated with irinotecan, and the incidence of cholinergic symptoms severe enough to interfere with treatment is quite low. In the series of Petit et al, the use of atropine was required in 34% of patients, and only one case of grade 3 early diarrhea occurred despite the use of a relatively high dose of irinotecan.[5]

Late Diarrhea

In contrast to early diarrhea, late diarrhea, defined as that occurring more than 24 hours after irinotecan administration, is a common and often serious and dose-limiting side effect. Although usually controllable with nonspecific and supportive measures, late diarrhea can be particularly dangerous in elderly or debilitated patients who experience other toxicities, such as neutropenia.[1]

Incidence

The overall incidence of late diarrhea in most US and European phase I and II trials of irinotecan ranges from 60% to 87% and appears to be dose-dependent.[1,9-11] The incidence of severe (National Cancer Institute [NCI] grade 3 or 4) diarrhea in these studies varies from 20% to 40%.[1,9-12] The incidence in Japanese studies is somewhat lower; however, most of these studies used less intensive dosing regimens.[13]

Timing

The onset and duration of late diarrhea may vary with the dosing schedule. In European studies in which patients received 350 mg/m^2 every 3 weeks, the median time to onset was 5 days and the median duration was 5 days.[11] In the pivotal American trials, in which patients received 125 mg/m^2/wk for 4 out of 6 weeks, the median time to onset was 11 days, and the median duration was 2 days (Figure 2).[14]

Predisposing Factors

Identification of patient characteristics that predispose to diarrhea may allow for the identification of patients who require close monitoring and early treatment. Unfortunately, this approach has not proven to be clinically useful.

In European studies, age older than 65 years, prior pelvic irradiation, and low performance status were significantly associated with an increased incidence of severe diarrhea.[1,3,11] In American studies, however, the results are conflicting. Von Hoff reported that ≥ 65 years was a risk factor for grade 3/4 diarrhea,[14] whereas Pazdur found no significant increase in these patients.[12] Schaaf et al uncovered no differences in irinotecan pharmacokinetics between patients older and younger than 65 years of age.[15]

Etiology

In normal states, intestinal fluids remain in homeostasis, maintaining a finely regulated balance between fluid secretion and absorption. The intestines receive 8 to 9 L of ingested and secreted fluids each day and absorb all but 100 to 200 mL.[16] Alteration of this balance by increased secretion or reduced absorption may result in the clinical symptom of diarrhea.

One potential mechanism by which drugs may induce diarrhea is direct damage to the intestinal epithelium. The resulting denuded mucosa is leaky and unable to absorb fluid. This is the probable mechanism of fluorouracil-induced diarrhea, which results from diffuse mucosal injury.[17,18] Alternatively, compounds may increase secretion or decrease absorption of fluid by intestinal epithelial cells.[16]

Irinotecan Pharmacology and Metabolism--Clues to the etiology of irinotecan-induced late diarrhea may be found in the complex pharmacology and metabolism of the drug (Figure 3). Irinotecan is a prodrug that is converted to an active form, SN-38, by carboxyl-esterases, which in humans are found predominantly in the liver.[19-21] The SN-38 metabolite is 250 to 1,000 times as potent an inhibitor of topoisomerase I as irinotecan.[22]

Inhibition of topoisomerase I, which correlates with antitumor activity, results in the formation of cleavable complexes in DNA,

which induce strand breaks.[23] This DNA damage is thought to lead to cell death by apoptosis,[24] which may be mediated through the interleukin-1 beta-converting enzyme (ICE) pathway.[25] Both irinotecan and SN-38 require an intact lactone ring for topoisomerase I inhibition. They are inactivated by pH-dependent hydrolysis of the ring to the hydroxy acid.[22,26]

SN-38 is further metabolized by glucuronidation to SN-38 glucuronide (SN-38G), which is inactive.[27,28]. Glucuronidation is specifically performed by the UGT*1.1 isoform of hepatic uridine diphosphate glucuronosyltransferase,[29] which also glucuronidates bilirubin and is deficient in Gilbert's syndrome.[30] The SN-38G metabolite can also be deconjugated back to SN-38 in the gut by bacterial glucuronidases, which may result in increased exposure of the intestinal epithelium to toxic products. Takasuna et al found a correlation between intestinal bacterial beta-glucuronidase activity and the site of epithelial damage in rats exposed to irinotecan.[31]

Biliary excretion is an important mechanism in the elimination of irinotecan and its metabolites, with 25%, 2%, and 1% of a dose excreted in the bile as irinotecan, SN-38G, and SN-38, respectively.[32] Levels of irinotecan and SN-38 in the bile are up to 113- and 40-fold higher than levels in plasma.[33] Normal excretion of these compounds into the bile is via the canalicular multispecific organic anion transporter (cMOAT), as well as other less-well characterized transporters.[34,35] Treatment with cyclosporine (Neoral, Sandimmune), which decreases biliary flow and inhibits MOAT, increases the areas under the curve (AUCs) of irinotecan, SN-38, and SN-38G severalfold.[36]

The relationship between the pharmacokinetics of irinotecan and its metabolites and diarrhea is also quite complex. Both the parent compound and metabolites undergo enterohepatic circulation, and the concentration of SN-38 has been correlated with diarrhea in mice[37] and in humans.[10,38,39] Ratain's group found that a calculated biliary index [$AUC_{CPT-11} \times (AUC_{SN-38}/AUC_{SN-38G})$] was predictive of diarrhea.[40,41] However, Conti et al did not find the biliary index or other pharmacokinetic parameters to correlate with diarrhea in patients dosed with irinotecan weekly.[10] The clinical usefulness of any of these measures is limited by the large overlap between putative high- and low-risk groups. Wasserman et al reported severe irinotecan toxicity in two patients with Gilbert's syndrome, in which glucuronida- tion is deficient.[42] This finding indicates the importance of glucuronidation in the detoxification of irinotecan and its metabolites. Patients with Gilbert's syndrome, which may be found in up to 6% of the general population,[43-45] may constitute a group at high risk for late diarrhea.

In rats, treatment with valproic acid, which competes for glucuronidation with SN-38, reduced SN-38G by 99% and increased the AUC of SN-38 by 270%.[46] Phenobarbital, an inducer of glucuronidation, increased the AUC of SN-38G while decreasing the AUCs of irinotecan and SN-38.[46]

Unresolved Questions--Several questions remain, however: Why is the gastrointestinal tract preferentially affected by irinotecan or its metabolites, and by what mechanism do they induce diarrhea? The excretion of biliary irinotecan and SN-38 may expose the intestinal mucosa to high levels of the compound responsible for late diarrhea.

Further investigation of late diarrhea has been hampered by the lack of a pathologic correlation with symptoms. There have been several animal studies revealing bowel injury,[31,47] but no comparable human reports, though human studies are under way. Ikuno et al reported that mice treated with irinotecan exhibited intestinal wall thinning with epithelial vacuolation, vascular dilatation, and an inflammatory cell infiltrate. There was evidence of apoptosis in the ileum, as well as epithelial cell hyperplasia with goblet cell metaplasia in the cecum.[47]

Interspecies variation may exist with respect to susceptibility to irinotecan toxicity. Guffroy and Hodge observed villous atrophy in the small intestine but not cecal lesions in their mouse studies.[48] Takasuna et al found characteristic intestinal changes that appeared in a time-dependent fashion in rats treated with irinotecan. Gross thinning of both the intestines and cecum was seen. Histologically, there was cell death and apoptosis with crypt dropout, followed by the development of severe submucosal edema and an inflammatory infiltrate.[31]

These results indicate that, at least in these models, diarrhea may result from a direct toxic action of irinotecan on the intestinal mucosa. One small human study of irinotecan-induced late diarrhea, reported in abstract form only, found normal d-xylose absorption, indicating a relatively intact intestinal mucosa[49] but increased clearance of alpha-1-antitrypsin, which is associated with protein-losing enteropathy.[50]

Other Effects of Irinotecan and Its Metabolites on the Intestinal Mucosa--Irinotecan and its metabolites may have additional effects on the intestinal mucosa that may induce diarrhea. In the normal intestine, secretion of fluid is driven by

active secretion of chloride.[51] Chloride is actively transported into the cell across the basolateral membrane by the Na^+:K^+:2Cl- cotransporter and then exits the cell via chloride channels along an electrochemical gradient.

In the rat, Sakai et al demonstrated that colonic chloride secretion, as measured with Ussing chambers as a short-circuit current, is stimulated by irinotecan.[52] This stimulation is mimicked by stable analogs of the unstable thromboxane A_2 and is blocked by inhibitors of cyclooxygenase, thromboxane synthase, and thromboxane A_2 receptors.[53] Our unpublished data show that SN-38 stimulates the short-circuit current in human colonic mucosa, indicating that a metabolite of irinotecan can induce chloride secretion. This effect is abrogated by cyclooxygenase inhibition.

Irinotecan may induce inflammation and intestinal secretion by paracrine mechanisms as well. Exposure of both mouse and human mononuclear cells to irinotecan induces secretion of tumor necrosis factor (TNF).[54] Expression of TNF is associated with AIDS-related diarrhea and induces chloride secretion in colonocytes.[55] Tumor necrosis factor also induces inflammation and may be important in the pathogenesis of inflammatory conditions, such as Crohn's disease.[56]

Therapy

Therapy

Nonspecific Measures--Nonspecific measures have proven partially effective in the treatment of irinotecan-induced late diarrhea. Abigereges et al showed that loperamide, an opiate analog, reduces the incidence of severe diarrhea when given in an intensive fashion.[57] This entails the administration of 2 mg of loperamide every 2 hours until the patient is free of diarrhea for 12 hours.

A modification of this regimen using a 4-mg initial dose and then 4 mg every 4 hours at night has become the standard for clinical studies and is recommended in the US clinical labeling for irinotecan.[58] Although no randomized studies of this loperamide regimen have been performed, the incidence of grade 3 and 4 diarrhea fell from 24% to 9% in patients so treated in American studies.[2] At these doses, loperamide probably reduces diarrhea by delaying intestinal transit, allowing increased time for fluid absorption.[16]

Opioids may also reduce fluid secretion by activating opioid receptors. Acetorphan, an enkephalinase inhibitor available in Europe, has also been used with some success in irinotecan-induced diarrhea in several small studies.[1,16,49,59]

Octreotide (Sandostatin), a synthetic, longer-acting analog of somatostatin available for the treatment of the symptoms of neuroendocrine tumors, reduces intestinal secretion and motility.[60] It may be useful in the treatment of severe fluorouracil-induced diarrhea.[61,62] Although octreotide has been used anecdotally in the treatment of irinotecan-induced late diarrhea, it has not been studied rigorously.

Rustum et al recently showed that treatment with the cytokine IL-15 significantly reduced the incidence of diarrhea and death without affecting antitumor activity in a rat model of irinotecan administration. The mechanism of this protective effect remains unclear.[63]

Other potential therapies are in various stages of development and study. Some have been used in other types of diarrhea, while others are specific to irinotecan. For example, the use of intestinal growth factors, such as keratinocyte growth factor (KGF), stem-cell factor, and glucagon-like peptide 2, is being explored to reduce the side effects caused by radiation and various types of chemotherapy.[64-66] Direct stimulation of intestinal stem cells by growth factors may reduce the extent and duration of mucosal damage and diarrhea. Multicenter trials assessing the efficacy of KGF in the prevention of fluorouracil-induced mucositis currently are under way (L. Rosen, personal communication, October, 1997).

Alteration of Irinotecan Metabolism--Another potential strategy to reduce irinotecan-induced late diarrhea is to alter the metabolism of the parent drug and its metabolites to reduce intestinal exposure to toxic compounds. The complex metabolism and pharmacokinetics of irinotecan offer a number of potential targets for manipulation.

Since SN-38G, the glucuronide of SN-38, appears to be an inactive metabolite, attempts have been made to alter glucuronidation. Gupta et al showed that phenobarbital administration increases glucuronidation of SN-38 in rats and lowers

plasma SN-38 concentrations.[46] Reductions in gastrointestinal toxicity have been noted in patients with neurologic malignancies treated with irinotecan. In one recent series of 60 glioma patients, most of whom were receiving antiseizure medications, no patient had severe diarrhea.[67] Certain antiepileptic drugs may induce UGT activity, while valproic acid decreases SN-38 glucuronidation in animal models.[46] Only one patient in this study was receiving valproate alone, and pharmacokinetic studies are currently under way.

In our experience treating 32 patients with brain malignancies with irinotecan at the University of California, Los Angeles, we found only two cases of grade 3 or 4 diarrhea. One of these patients was taking valproic acid alone, while the other was not receiving any antiepileptics (T. Cloughesy, personal communication, October, 1997). Most other drugs tested so far, however, have had little effect on glucuronidation of SN-38.[20]

Glucuronidation of SN-38 may also be reduced by inhibiting bacterial glucuronidase activity in the gut. Treatment of rats with orally administered penicillin and streptomycin eliminated bacterial deconjugation of SN-38G in the stool and ameliorated mucosal damage and diarrhea.[31]

Another method of reducing glucuronidase has been the use of traditional Japanese herbal (Kampo) medications. These medications contain various natural glucuronides, such as baicalin, which can inhibit bacterial glucuronidases[68,69] and reduce diarrhea in animal studies. Although increasing glucuronidation of SN-38 in the intestinal lumen may improve diarrhea, it is unclear what effects this may have on plasma SN-38 levels and therapeutic efficacy.

Reducing the excretion of toxic metabolites into the gastrointestinal tract may also affect late diarrhea. As previously mentioned, drugs such as cyclosporine may inhibit biliary excretion of irinotecan and its metabolites.[36] Human trials are under way to determine the pharmacokinetic and side effect profile of the coadministration of cyclosporine and irinotecan.[70]

Chronobiologic modulation may offer a means of reducing irinotecan-induced toxicity. In animal studies, Ohdo et al showed that bone marrow toxicity and pharmacokinetics of irinotecan were circadian-rhythm-dependent in mice. [69] Gallbladder emptying, which occurs in a daily pattern, is stimulated by eating via release of cholecystokinin from and activation of neural pathways in the small intestine.[72] Proper timing of irinotecan dosing could possibly alter the drug's metabolism and reduce intestinal exposure to toxic metabolites, although this has not been studied.

Another theoretical method to ameliorate irinotecan-induced diarrhea would be to alter the proportion of active irinotecan and SN-38 in the lumen by reducing the proportion in the lactone form. This conversion is pH-dependent,[26] and altering stool pH may be another pathway for the effects of antibiotics on late diarrhea.

Finally, the cytoprotectant amifostine (Ethyol) specifically reduces DNA damage by preferentially scavenging free radicals in nonmalignant cells. Amifostine has been shown to reduce the toxicities of radiation, cisplatin (Platinol), and alkylating agents in normal tissues.[73] Although the effects of irinotecan do not appear to be mediated by the generation of free radicals, a phase II trial of the combination of irinotecan and amifostine is currently under way (D. Prager: personal communication, October, 1997).

Blockade of Irinotecan-Induced Fluid Secretion—If irinotecan-induced secretion is responsible for at least part of the pathophysiology of late diarrhea, specific inhibitors may be useful therapeutically. In animal models, thromboxane A_2 appears to be important in the induction of increased chloride excretion. One method of reducing thromboxane A_2 would be to block cyclooxygenase-mediated metabolism of arachidonic acid to prostaglandin H_2, which is required for thromboxane synthesis. [74] Although indomethacin blocks irinotecan-induced colonic chloride secretion in vitro,[53] nonspecific cyclooxygenase inhibitors have a high incidence of gastrointestinal and hematologic side effects.[75] The use of specific cyclooxygenase 2 inhibitors, which will soon be available, may avoid the gastrointestinal toxicities of nonspecific inhibitors.[76] Another option would be to use specific thromboxane synthase inhibitors, some of which are already approved for the treatment of asthma in Japan.[77]

Conclusions

The activity of irinotecan against a broad spectrum of malignancies heralds the widespread use of this important new chemotherapeutic drug. With increasing experience, the gastrointestinal toxicities of irinotecan have become better defined and at least partially managed.

Despite the advent of high-dose loperamide therapy, late diarrhea remains a major dose-limiting toxicity, resulting in significant patient morbidity and occasional mortality. The work of Japanese, American, and European investigators has hinted at potential mech- anisms of and possible therapies for late diarrhea. Additional animal and human studies are required to specifically identify underlying causes and potential therapies.

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OTHER NEWS TO NOTE

• **Advancis Pharmaceutical Corp.**, of Germantown, Md., said it expects to start enrolling 600 patients later this month for a new Phase III trial of Amoxicillin Pulsys in adults and adolescents with pharyngitis/tonsillitis. The company concluded a pre-Phase III meeting with the FDA, and the regulatory strategy was acceptable to the agency. If the trial is successful, it will support a new drug application filing in late 2006. The product missed in two pivotal trials earlier this year, leading to a staff reduction and a dropped partnership. (See *BioWorld Today*, Sept. 16, 2005.)

• **Amazon Biotech Inc.**, of New York, is preparing an investigational new drug for a cancer drug candidate believed to be useful in early stage breast cancer. Some of the active ingredients have shown anticancer efficacy in in vitro studies. Amazon Biotech is a natural plant pharmaceutical company primarily developing immune modulator drugs.

• **American BioScience Inc.**, of Santa Monica, Calif., said clinical data of Abraxane showed high response rates in patients with non-small-cell lung cancer, metastatic malignant melanoma and head and neck cancer. Abraxane is an albumin-bound drug designed to work by using tumors' attraction to albumin to kill the cancer. The data were presented at the Chemotherapy Foundation Symposium XXII in New York.

• **Angiotech Pharmaceuticals Inc.**, of Vancouver, British Columbia, entered a definitive agreement to acquire the Lifespan ePTFE vascular graft business in Laguna Hills, Calif. from **Edwards Lifesciences Corp.** for $14 million in cash. The agreement includes an arrangement in which Edwards will retain certain rights to distribute the existing Lifespan product line globally for up to five years, as well as become the exclusive distributor of Angiotech's Vascular Wrap paclitaxel-eluting mesh products in the European Union for up to three years following regulatory approval.

• **Bayer Pharmaceuticals Corp.**, of West Haven, Conn., and **Onyx Pharmaceuticals Inc.**, of Emeryville, Calif., said that Bernard Escudier provided an update on the Nexavar (sorafenib tosylate) Tablets Phase III trial in patients with advanced renal-cell carcinoma (RCC), or kidney cancer during the 13th European Cancer Conference (ECCO) in Paris. Escudier reported, based on an interim analysis, that there was an estimated 39 percent improvement in survival for patients receiving Nexavar vs. those receiving placebo (p=0.018, hazard ratio 0.72). More than 900 patients with advanced kidney cancer participated in the international Phase III study.

• **Celgene Corp.**, of Summit, N.J., said preliminary Phase II data comparing the efficacy and safety of the combination of thalidomide and topotecan vs. topotecan alone show that the addition of thalidomide could slow the growth of recurrent epithelial ovarian cancer in patients who had received prior treatments. Results showed that patients in the topotecan plus thalidomide arm reported an overall response rate of 50 percent, compared to 22 percent of patients receiving topotecan alone, and 32 percent of patients receiving both products showed a complete response vs. 16 percent of those in the topotecan arm. These data were presented at the XXIII Chemotherapy Foundation Symposium in New York.

• **Chromos Molecular Systems**, of Burnaby, British Columbia, said it entered a definitive agreement under which it will acquire **Targeted Molecules Corp.**, of San Diego, which is focused on the development of antibody product candidates for treatment of multiple sclerosis and acute thrombosis. Chromos also will complete a private placement to raise not less than $6 million, the proceeds of which will be used to finance operations. As a result of the acquisition, Chromos will gain two humanized monoclonal antibody product candidates, TMC-2003 for inflammatory diseases and NHAT for acute thrombosis. TMC has demonstrated efficacy of those candidates in preclinical proof of principle studies. TMC-2003 (to be re-designated CHR-1103) is a humanized monoclonal antibody directed to VLA-2, an integrin involved in maintenance of inflammation.

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